PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SARM-1	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/FI2004/000387	International filing date *(day/month/year)* 24.06.2004	Priority date *(day/month/year)* 27.06.2003
International Patent Classification (IPC) or national classification and IPC C07C235/24, C07C255/58, C07D213/68, A61K31/395, A61K31/277, A61K31/167, A61P5/26, A61P15/16		
Applicant ORION CORPORATION et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.04.2005	11.07.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Seelmann, M Telephone No. +49 89 2399-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/FI2004/000387

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-64	as originally filed
Claims, Numbers	
1-11	as originally filed
Drawings, Sheets	
1/1	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4,7
	No:	Claims	1-3,5-6,8-11
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-11
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

D1 WO 03 06 59 92 P-document
D2 WO 03 04 96 75
D3 US 2002 00 99 096
D4 US 4 636 505

Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 Novelty - Art.33(2) PCT

Propionamide derivatives are already known from the prior art documents **D1** to **D4** and all as androgen receptor modulators.

D1 and **D2** describe propionamide derivatives of formulae overlapping with the one of formula (I) of the present application (D1, claims 6 and 8; D2, claims 3-5, 7-10, 15). Both documents disclose more specifically compounds wherein: R1 = $C(Alkyl)_3$; R2 = CN or NO_2; R4 = OH, O-Alkyl; R3 = Alkyl or Haloalkyl; X = O or NH and A = substituted phenyl.

The closest related propionamide derivatives of **D3** are in example 2, Gtx-014 to GTx-017 or claims 12, 14, 16 and 18 wherein R1 is CF_3 instead of being Me for the present application.

The closest related propionamide derivatives of **D4** are given in the table on column 9 and concern entries 20, 25 and 26 differing from the compounds of formula (I) in that either R1 is CF_3 instead of being Me or X = S instead of being O.

Novelty is accordingly not recognized for the subject-matters of claims 1-3, 5-6 and 8-11.

V.2 Inventive step - Art.33(3) PCT

The claims 1-11 do not appear to fulfill the requirements of Article 33(3) EPC for the following reasons:

The closest related propionamide derivatives are known from **D3** (example 2, Gtx-014 to GTx-017 or claims 12, 14, 16 and 18). It differs structurally in that R1 is $-CF_3$ instead of being $-CH_3$ for the present application. The present technical problem posed is to provide further androgen receptor modulators. The solution proposed are the ones of formula (I). The binding AR activity was provided in the present application for compounds characterized by R1 = Me or Et, R2 = NO_2, R4 = H and X = O (test 1). Angonist / antagonist activity was investigated on one single compound A of example 3: R1 = Me, R2 = NO_2, R3 = Me, R4 = H, A = 4-(Me-CO-NH)-3-F-Ph and X = O (test 2).

2.1 If the structural modification of R1 from a trifluoromethyl to a methyl group could not have been anticipated by the man skilled in the art to not affect the pharmaceutical property of the compound, then other modifications as provided in claim 1 can not be expected without further experimental proof. Accordingly the technical problem has not been solved over the entire scope of protection sought.

2.2 In view of the extremely close structural relationship, modification of a methyl to a trifluoromethyl group, to **D3/D4** compounds it is considered that the man skilled in the art would regard the new compounds of this application as being obvious alternatives to the known compounds. In this regard **D4** discloses the entries 20, 25 and 26 bearing either a methyl or a trifluoromethyl group as substituent on the phenyl group and all possessing the same activity ! Therefore, the problem underlying the present application should be seen in the provision of new derivatives having unexpected properties over those of the closest prior art compounds (**D3/D4**). In the absence of comparative test results or other appropriate information it is not possible to decide whether such a problem has been solved or not. In the case where comparative tests are envisaged in order to support an inventive step, these must be carried out between the compound A of the present application and the compounds of the closest prior art having the maximum structural similarity, i.e. Gtx-017 of **D3** and entry 20, col.9 of **D4**, such that the effect is shown to have its origins in the distinguishing feature of the claimed invention.

2.3 As discussed above, it is convincingly shown that the compound A does actually show the alleged properties. In other words, further definitions as described in claim 1 cannot be considered as a reasonable generalisation of this example. Every

generalisation of the examples, however, would not be allowed under Article 34(2)b) PCT.

V.3 Industrial applicability

For the assessment of the presently worded claims 9-11 on the question whether their subject-matter is industrially applicable, no unified criteria exist in PCT. The patentability under national patent laws can also be dependent on the formulation of the claims. The EPO, for example, does not recognize the subject-matter of claims to the use of a compound in medical treatment as being industrially applicable, but will allow, however, claims to a known compound for first medical use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.